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Small molecule modulators of RING-type E3 ligases: MDM and cullin families as targets

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Abstract

© 2018 Bulatov, Zagidullin, Valiullina, Sayarova and Rizvanov. Ubiquitin-proteasome system (UPS) is a primary signaling pathway for regulation of intracellular protein levels. E3 ubiquitin ligases, substrate-specific members of the UPS, represent highly attractive protein targets for drug discovery. The importance of E3 ligases as prospective targets for small molecule modulation is reinforced by ever growing evidence of their role in cancer and other diseases. To date the number of potent compounds targeting E3 ligases remains rather low and their rational design constitutes a challenging task. To successfully address this problem one must take into consideration the multi-subunit nature of many E3 ligases that implies multiple druggable pockets and protein-protein interfaces. In this review, we briefly cover the current state of drug discovery in the field of RING-type E3 ligases with focus on MDM and Cullin families as targets. We also provide an overview of small molecule chimeras that induce RING-type E3-mediated proteasomal degradation of substrate proteins of interest.

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Keywords

Cullin family, Induced protein degradation, MDM family, PROTACs, RING-type E3 ligases, Small molecules, SNIPERs, Ubiquitin-proteasome system

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